English Translation of JP A 61-263917

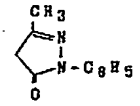
Specification

1. Title of the Invention

Cerebral Normalizing Agent

2. Claims

A cerebral normalizing agent characterized by comprising as an active ingredient, 3-methyl-1-phenyl-2-pyrazolin-5-one of the formula:



or a pharmaceutically acceptable salt thereof.

3. Detailed Description of the Invention

[Field to which the Invention is industrially applied]

This invention relates to a cerebral normalizing agent, more particularly to a cerebral normalizing agent comprising as an active ingredient, 3-methyl-1-phenyl-2-pyrazolin-5-one or a pharmaceutically acceptable salt thereof.

[Prior Art and Problems to be solved]

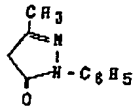
In various cerebral diseases such as cerebrovascular disorders, cerebral dysfunctions, vascular dementia, cerebrovascular tissue lesions accompanied with aging, etc., symptoms such as consciousness disorders, lowering in memory, etc., based on cerebral dysfunctions, namely the abnormal pattern of electroencephalogram will be caused. Therefore, as the medicine to be used for prophylaxis and therapy of these cerebral disorders, those having antagonistic action against drowsy pattern of electroencephalogram during cerebral function abnormality (abnormal electroencephalogram) (hereinafter referred to as "electroencephalogram normalizing action") have been desired.

As a medicine having such pharmacological activity, thyrotropine releasing hormone (TRH) having a chemical structure of L-pyrroglutamyl-L-histidyl-L-prolineamide has been known [Neuropharmacology, 14, 489 (1975); Journal of Pharmacology and Experimental Therapeutics 193, 11 (1975)]. However, TRH exhibites an action which is deemed to be a side action in clinic, also against electroencephalogram under normal state. Also, since TRH is a tripeptide, there is a fear that it has a problem in stability in living body or absorption by oral administration, and the dosage form at the present time is only by way of intravenous administration.

On the other hand, in the above-mentioned cerebral diseases, it is considered that ischemia in cerebral tissues based on the vascular disorders is an important factor.

Therefore, it is preferable that the agent for prophylaxis and therapy of the above-mentioned diseases has both an electroencephalogram normalizing action and a cerebral ischemia protective action.

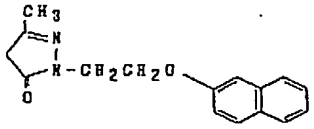
On the other hand, 3-methyl-1-phenyl-2-pyrazolin-5-one of the formula (I):



(I)

is a metabolite of antipyrine [Drug Metab. Dispos., 6, 228 (1978)]. Although this is a known compound used for a raw material of dye, it is not known that this compound can be used for a pharmaceutical.

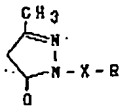
Japanese Unexamined Patent Publication No. 13766/1976 discloses a pyrazolin-5-one derivative represented by the following formula (II):



(II)

and its use as antithrombus agent.

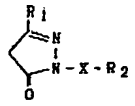
Japanese Unexamined Patent Publication No. 175469/1984 discloses a use of a pyrazolin-5-one derivative of the following formula (III):



(III)

(wherein X represents a group $-CH_2CH_2S-$, etc., and R represents an aryl group) as a lipoxygenase inhibitor.

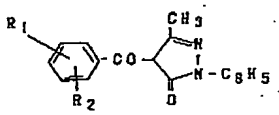
Japanese Patent Publication No. 512/1984 discloses a use of a pyrazolin-5-one derivative of formula (IV):



( IV )

(wherein $R_1$ represents a hydrogen atom or an amino group, $R_2$ an aryl group and X represents a group $-CH_2CH_2-$, etc.) as a diuretic, antihypertensive, and antithrombosis: However, these derivatives are not of the type in which all the aryl groups are bonded directly to the 1-position of the pyrazolin-5-one nucleus, and there is no description about the effect on cerebral dysfunctions including electroencephalogram normalizing action at all.

Also, West Germany Patent No. 28 36 891 discloses a pyrazolin-5-one derivative of the following formula (V):



( V )

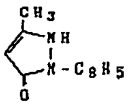
(wherein $R_1$ and $R_2$ represent a hydrogen atom or a substituent). However, this document merely discloses its use as antiinflammatory agent.

Accordingly, the present inventors have studied intensively in order to provide a cerebral normalizing agent having a cerebral ischemia protective action in addition to an electroencephalogram normalizing action, which can be orally administered. Consequently, they have found that 3-methyl-1-phenyl-2-pyrazolin-5-one of the above-mentioned formula (I) has a cerebral ischemia protective action in addition to an electroencephalogram normalizing action although it shows little anti-inflammatory action that the similar compound shown by the above-mentioned formula (V) shows. The present invention has been accomplished on the basis of such a finding.

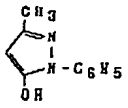
[Constitution of the Invention]

The cerebral normalizing agent of the present invention is characterized by comprising as an active ingredient, 3-methyl-1-phenyl-2-pyrazolin-5-one of the above-mentioned formula (I).

The compound (I) to be used in the present invention can also take the structures shown by the following formula (I') or (I"):



( I' )



( I" )

Accordingly, the compounds having the structure of the above formula (I') or (I") are also included within the active ingredient of the present invention.

Pharmaceutically acceptable salts of the compound (I) to be used in the present invention include salts with mineral acids such as hydrochloride acid, sulfuric acid, hydrobromic acid, phosphoric acid, etc.; salts with organic acids such as methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, acetic acid, glycolic acid, glucuronic acid, maleic acid, fumaric acid, oxalic acid, ascorbic acid, citric acid, salicylic acid, nicotinic acid, tartaric acid, etc.; salts with alkali metals such as sodium, potassium, etc.; salts with alkaline earth metals such as magnesium, calcium, etc.; salts with amines such as ammonia, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)-piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, L-glucamine, etc.

The compound (I) to be used in the present invention is a known compound which is used as starting materials for dyes. And, this compound has been already evidenced to be high in safety (mouse intraperitoneal administration LD50 2012 mg/kg; rat oral administration $LD_{50}$ 3500 mg/kg) [Registry of Toxic Effects of Chemical Substances, 1981-1982] and also free from carcinogenicity [National Cancer Institute Report, 1978, 89].

The compound (I) is commercially available (from Wako Pure Chemical Industries, Inc. or Tokyo Kasei Kogyou Co., Ltd.), but can be synthesized according to the followings and used.

That is, the compound (I) can be prepared by allowing ethyl acetoacetate and phenylhydradine to react in the presence or absence of a solvent, optionally in the presence of a catalyst such as a base or an acid [Beilstein, 24, 20].

In applying clinically the compound (I) in the case of using it orally, it is preferable to administer the compound (I) at a dose of 1 to 100 mg 1 to 3 times/day for an adult (human). In the case of intravenous injection, it is preferable to administer the compound (I) at a dose of 0.01 to 10 mg 2 to 5 times/day for an adult or to inject these doses continuously by way of instillation. On the other hand, in the case of intrarectal administration, it is preferable to administer the compound (I) at a dose of 1 to 100 mg 1 to 3 times/day. It is more preferable to increase or decrease adequately the above doses depending on the age, the condition and specifics of the patient and/or the specifics of the disease and symptoms. Other mammals would be treated within the same dosage range modified for relative body weight.

Also, in the case of oral or intrarectal administration, the compound may be used as a delayed-release preparation.

In forming preparations, it is generally practiced to use a composition containing the compound (I) or at least one pharmaceutically acceptable salts thereof together with a

carrier, excepient or other additives for pharmaceuticals conventionally used. Pharmaceutical carriers may be either solid or liquid, and examples of solid carriers include lactose, kaolin, sucrose, crystalline cellulose, corn starch, talc, agar, pectin, acacia, stearic acid, magnesium stearate, lecithin, sodium chloride, etc.

Examples of liquid carriers include syrup, glycerine, peanuts oil, polyvinylpyrrolidone, olive oil, ethanol, benzyl alcohol, propyleneglycol, water, etc.

Various preparation forms can be employed and, when using a solid carrier, they can be formed into tablets, powders, granules, hard gelatin capsules, suppositories or troches. The amount of the solid carrier can be widely varied, but it is preferably about 1 mg to about 1 g.

When employing a liquid carrier, it can be made into a syrup, emulsion, soft gelatin capsules, further sterilized injectable solutions or aqueous or non-aqueous suspensions filled in ampoules.

Also, the compound (I) can be also used as a cyclodextrin clathrate compound thereof or through procedure of incorporating it in a liposome.

[Effect of the Invention]

The cerebral normalizing agent of the present invention has a cerebral ischemia protective action in addition to an electroencephalogram normalizing action, and can be orally administered, and is widely applicable for therapy of trauma at the head portion, intracerebral hemorrhage, subarachidonic hemorrhage, cerebral arterio-sclerosis, cerebral infarction, cerebral embolism, etc.; therapy at the acute stage of ischemic cerebrovascular disorders caused by said diseases such as cerebral edema, etc.; thereby and prevention of recurrence of various diseases recognized at the subacute stage and chronic stage of cerebrovascular disorders after elongation of life after elapse of said acute stage, such as lowering in cerebral dysfunctions, typically vascular dementia, etc.; therapy of various cerebral diseases complicated by the advance of cerebrovascular tissue lesion accompanied with aging; clearing of obnubilation which appears at the acute stage and chronic stage of cardiovascular disorders; as well as emergence from anesthesia, etc.

Also, it has a specific feature, as different from TRH, of normalizing selectively only the electroencephalogram under abnormal state substantially without exhibiting any action on the electroencephalogram under normal state.

[Examples of the Invention]

The present invention is described in more detail by referring to synthetic examples and examples, but these are not intended to limit the scope of the present invention.

Synthetic Example

Into 50 ml of ethanol, 13.0 g of ethyl acetoacetate and 10.8 g of phenylhydrazine were added, and the mixture was refluxed under stirring for 3 hours. After left to cool, the precipitated crystals were filtered and recrystallized from ethanol to obtain 11.3 g of 3-methyl-1-phenyl-2-pyrazolin-5-one as colorless crystals.
Yield 65%, m.p. 127.5°C-128.5°C

Example 1

(1) Antagonistic action against drowsy pattern of electroencephalogram induced by phenobarbital sodium salt

A Wistar-strain male rat weighing about 400 g was intramasculary administered with 0.6 mg of d-tubocurarine to be immobilized and, while maintaining the rectal temperature at 37°C to 38°C under artificial respiration, the electroencephalogram of the left cerebral frontal cortex was measured and recorded. Also, within the left femoral artery and vein, cannulas for measurement of artery pressure and for administration of medicine were placed, respectively.

The active ingredient of the present invention was used in the form of sodium salt and the respective doses of said active ingredient and 30 mg/kg of phenobarbital sodium salt (produced by Iwaki Seiyaku K.K.) (hereinafter called "PB") were each dissolved in physiological saline and administered intravenously in a liquid amount of 1 ml/kg.

The action of the active ingredient of the present invention affecting the cortex electroencephalogram after PB administration was investigated as follows; Namely, at the time of 5 minutes or later after PB administration when increase of the slow-wave component can be clearly recognized on electroencephalogram, 1, 3, 10, 30 and 100 mg/kg of the active ingredient were administered at 5-minute intervaqls. To the control group 1 ml/kg of physiological saline was intravenously administered.

Recording and analysis of electroencephalogram were continuously drawn together with artery pressure, heart rate and rectal temperature on the recorder through a multi-purpose monitoring recording device (model RM-85, produced by Nippon Koden K.K.). At the same time, electroencephalogram was recorded in data recorder (model A-65, produced by Sony K.K.), and compressed spectral array analysis was conducted by means of a computer for medical data processing (ATAC-450, produced by Nippon Koden K.K.).

By administration of 30 mg/kg of PB, the cerebral cortical electroencephalogram becomes high voltage slow-wave, thus exhibiting clearly sleep-like electroencephalogram. Such an action persists for at least 3 hours or longer after the administration.

In contrast, when the active ingredient of the present invention wasadministered

even in an amount of 100 mg/kg, not only the drowsy pattern of electroencephalogram as observed in the case of PB, but also no appearance of low voltage fast-wave component (arousal pattern) was recognized at all.

From this fact, it has been found that the active ingredient of the present invention has no effect on normal electroencephalogram at all even when administered in a large amount.

However, when the active ingredient of the present invention was administered during appearance of the drowsy pattern of electroencephalogram after PB administration, the drowsy pattern of electroencephalogram was normalized depending on the dose thereof. The results are shown in Table 1.

Table 1

| Administered group | Results |
|---|---|
| Active ingredient of the invention | Antagonistic action at 1 mg/kg or higher |
| Control group | No antagonistic action |

(2) Protective action in cerebral ischemia recirculation model

A Wistar-strain male rat weighing about 400 g was administered intramascularly with 0.6 mg of di-tubocurarine to be immobilized and, after a trachea cannulation, the head portion was fixed under artificial respiration on a stereotaxic device. The head skin was cut open, cranial bone was bored, and then bipolar electrode for lead-out of electroencephalogram were placed on the surface of the subdural left frontal cerebral cortex. After the electrode was fixed with the cranial bone by use of dental cement, the animal was held on its back. Next, a cannula for measurement of systemic pressure was placed within the left femoral artery, and a cannula for additional administration of d-tubocurarine within the left femoral vein, respectively. The heart rate was measured and recorded by driving a heart rate meter with the artery wave.

After blood pressure, heart rate and various parameters of electroencephalogram were stabilized, the active ingredient (free type) of the present invention having each concentration that was prepared in a suspension so as to give 1 ml/kg in 1% tragacanth gum solution was administered directly into duodenum 30 minutes after cerebral ischemia loading. To the control group, only the 1% tragacanth gum solution of the same volume was

administered similarly.

Ten to twenty minutes after administration of the medicine, while monitoring the electroencephalogram, blood pressure and heart rate on a multi-purpose monitoring recording device (RM-85 model, produced by Nippon Koden K.K.), the following operations were performed according to the methods shown below for cerebral ischemia loading.

First, ribs were set free at the left costicartilage end to open the chest. Next, cerebral blood flow was blocked for ten minutes by obstructing the left common carotid artery and the left subclavian artery exposed at the aorta originating portion at the same time, and then the brachiocephalic trunk by use of artery clips 30 minutes after administration of the medicine.

Recirculation of cerebral blood flow was effected by releasing at the same time the two artery clips mounted on the respective sites as mentioned above.

The protective action of the medicine for the disorder after recirculation of cerebral ischemia was examined by the presence of restoration of electroencephalogram, and survival time of animal after the recirculation.

During the experiment, the rectal temperature of the animal was maintained at 37°C to 38°C by use of a warming mat. Also, the rectal temperature was continuously drawn on the recorder together with electroencephalogram, femoral artery pressure and heart rate.

When cerebral ischemia was loaded for 10 minutes, the voltage of electroencephalogram was lowered immediately after ischemia until electroencephalogram became disappeared and leveled after elapse of about 15 seconds. Such flattening of electroencephalogram during loading of ischemia was recognized commonly in both of the control group and the group administered with the active ingredient of the present invention.

Even when cerebral ischemia for ten minutes was released and recirculated, no appearance of electroencephalogram was recognized at all in all the cases of the control group and flattering of electroencephalogram was continued to be maintained similarly as during loading of ischemia. By persistence of such a flattened electroencephalogram, the animals were dead 75 minutes after recirculation on an average.

However, in the group administered with the active ingredient of the present invention, electroencephalogram appeared by restoration during recirculation period, whereby the function of the cardiovascular system were activated and normalized simultaneously with restoration of the so called cerebral functions. As the overall results of these, the survival time of animals after recirculation was clearly elongated. The results are shown in Table 2.

Table 2

| Administered group | | Animal No. | Survival time after recircuration (min.) | Presence of electroence-phalogram restoration | Judgment of action* |
|---|---|---|---|---|---|
| Active ingredient of the invention | 3 mg/kg | 1 | 85 | + | + |
| | | 2 | 126 | - | - |
| | | average | 106 | | |
| | 10 mg/kg | 1 | 46 | + | + |
| | | 2 | 140 | + | + |
| | | 3 | 164 | + | + |
| | | average | 117 | | |
| Control group | | 1 | 54 | - | - |
| | | 2 | 70 | - | - |
| | | 3 | 74 | - | - |
| | | 4 | 76 | - | - |
| | | 5 | 100 | - | - |
| | | average | 75 | | |

*The case when restoration of electroencephalogram is recognized is judge as +, and the case when not recognized as -.

Example 2

Preparation of the cerebral normalizing agent of the present invention

(1) Tablets

The following components were mixed in a conventional manner and tabletted by means of a conventional device.

| | |
|---|---|
| Active ingredient of the invention | 10 mg |
| Crystalline cellulose | 21 mg |
| Corn starch | 33 mg |
| Lactose | 65 mg |
| Magnesium stearate | 1.3 mg |

(2) Soft capsules

The following components were mixed in a conventional manner and filled in soft

capsules.

| | |
|---|---|
| Active ingredient of the invention | 10 mg |
| Olive oil | 10.5 mg |
| Lecithin | 6.5 mg |

(3) Preparation for injection

The following components were mixed in a conventional manner and 1 mg ampoules were prepared.

| | |
|---|---|
| Active ingredient of the invention | 0.7 mg |
| Sodium chloride | 3.5 mg |
| Distilled water for injection | 1.0 ml |